The Therapeutic Role of Interferons and Monoclonal Antibodies in Cutaneous T-Cell Lymphomas

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The discovery of recombinant DNA and hybridoma technologies led to the ability to mass produce proteins of the immune system. Interferons and monoclonal antibodies are among the first immune proteins which have been tested as anti-tumor agents. The interferons can be divided into three major classes, alpha, beta, and gamma, which have both similarities and differences in their mechanism of action [1,2]. The alpha and beta interferons share the same cell surface receptors. The alpha interferons were tested clinically prior to the beta interferons. As yet, there are no clinical situations in malignant disorders where beta interferons are preferred over alpha interferons. The recombinant gamma interferons have been tested in many malignancies. Because the alpha and gamma interferons have different receptors, different mechanisms of action, and are additive or synergistic in in vitro assays, the combination is currently in clinical trials for some malignancies [1].

Monoclonal antibodies that react with cell surface antigens of normal and malignant T cells are numerous. The function of many of these is known. Some are important in T-cell activation, some in T-cell proliferation, some in antigen recognition, and many have no known function. Several of these antibodies have been evaluated for their potential utility in imaging and treating malignant T-cell disorders [3–11].

Mycosis fungoids and the Sezary syndrome are low-grade T-cell non-Hodgkins lymphomas with initial manifestations in the skin. They are characterized by a malignant proliferation of helper T cells and are often referred to collectively as cutaneous T-cell lymphomas [12,13]. Because of their cutaneous presentation, initial therapies such as topical chemotherapy, electron irradiation, and phototherapy are directed at the skin [12]. However, systemic progression is inevitable and systemic chemotherapy provides only temporary palliation. Even the initial combination of systemic combination chemotherapy and whole skin electron irradiation fails to improve survival over more conservative approaches [14].

The availability of recombinant interferons and hybidoma monoclonal antibodies led to their evaluation in these lymphomas. The results of these trials are reviewed in this manuscript.

THE ROLE OF INTERFERONS IN CUTANEOUS T-CELL LYMPHOMAS

Initial studies evaluated recombinant alpha interferons in heavily pretreated patients with cutaneous T-cell lymphomas. The first trial from the National Cancer Institute evaluated recombinant interferon alpha-2a (rIFNα2a) given at maximally tolerated dose determined from Phase I clinical trials (50 MU/m²) IM or SQ, three times weekly) [15,17] (Tables I and II). This series of 20 patients had primarily advanced stages, and all were heavily pretreated with more than one therapy. Chemotherapy had been given to 16 of the 20 patients. Despite the poor prognosis of this group, nine (45%) had an objective response, including three complete and six partial responses. The median response duration was 6 months, but all three complete responses lasted more than 1 year [17]. In addition, five patients had mixed or minor responses which lasted for a median of 3 months. Stable disease and progressive disease within 3 months were noted in three patients each. Toxicity on this regimen was considerable. A flu-like syndrome consisting of fever, chills, malaise, anorexia, and weight loss occurred in all patients and necessitated a 50%-90% dose reduction. Patients inevitably developed a tachyphylaxis to the toxicities, and continuing side effects after 1 month were rare. Additional toxicities were elevations in hepatic enzymes (two patients), lowering of leukocyte or platelet counts (two patients), and a reversible nephrotic syndrome in one patient. These toxicities suggested that future trials should evaluate other dose schedules and established a role for interferon in these lymphomas.

A second trial from the National Cancer Institute (NCI) [18] evaluated another high-dose rIFNα2a regimen (Table I). In this trial, patients received 10 MU/m² IM on day 1 and 20 MU/m² IM on days 2–5, every 3 weeks for 4 cycles. Stable and responding patients were then escalated to 20 MU/m² on day 1 and 100 MU/m² on days 2–5, every 3 weeks. This trial was also conducted in advanced stage, heavily pretreated patients. The overall response rate (29%) in this trial was similar but slightly lower than the response rate in the initial trial. The amount of interferon actually delivered was similar in the two regimes (Table I). This trial confirmed the activity of recombinant alpha interferon but did not increase the response rate or abolish the toxicity.

The groups from Northwestern and Duke Universities evaluated a low dose interferon (3MU/m² daily) and compared this to an intermediate dose regimen where patients were started at 3 MU/m² and rapidly escalated to 36 MU/m², depending on tolerance [19] (Table II). This trial was designed as a randomized trial to directly compare a low-dose versus an intermediate dose. There were too few patients and too many dose changes to draw firm conclusions on dose, although most responses occurred above the 3-MU dose level. Overall, there were 15 responses in the 22 patients (68%). The responses lasted 4–28 months in a group of patients which was more favorable than the NCI series.

A small series of patients from Temple University received intralesional or low-dose systemic recombinant alpha 2b interferon [20]. None of five patients receiving systemic therapy had an objective response within the first four weeks of therapy. It is possible that the low-dose or the short duration of therapy led to the lack of response in this series.

There are three studies which used an intermediate dose of recombinant alpha interferon [21–23]. Each of these started with a

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Abbreviations:
CTCL: cutaneous T-cell lymphoma
IM: intramuscular
NCI: National Cancer Institute
PUVA: psoralin plus ultraviolet A light therapy
rIFNα2a: recombinant interferon alpha 2a
SQ: subcutaneous

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Table I. High-Dose rIFN α2a in Advanced Refractory Cutaneous T-Cell Lymphomas

	50 MU/m² TIW[a]	10 MU/m² d1[b] 50 M/m² d2–5
Number of patients	20	24
Number of complete response	3	1
Number of partial response	6	6
Number minor/mixed response	5	
Median duration response	6	8
Range (months)	(3–36+)	(4–19)

[a] References [16,17].
[b] Reference [18].

low dose (3 MU), which was escalated to 18–36 MU according to patient tolerance. Each of these series had excellent results, with response rates of 75%-85%. In the series of Tura et al the majority of patients were advanced stage and previously treated [21]. The response rate was an impressive 80%, with three complete and nine partial responses among 15 patients [21]. Covelli et al observed an 85% response rate (five complete and eight partial) among 20 patients who were untreated and primarily early stage [22]. The responses lasted for a median of more than 1 year in this trial. In a similar but smaller series, Thestrup-Pedersen et al reported three partial responses among four patients [23]. These authors also found impressive responses when alpha interferon was combined with etretinate.

There has been one trial evaluating recombinant gamma interferon in cutaneous T-cell lymphomas which was conducted at the University of Colorado and Northwestern University [24] (Table II). In this series the patients were largely heavily pretreated and in advanced stages, as in the early NCI series with alpha interferon. There were five partial responses among 16 patients for a 31% response rate. Toxicity was similar to that observed with alpha interferon. The dose of the gamma interferon (0.25–0.5 mg/m²) was slightly above the dose subsequently shown to be the optimal biologic dose. It is clear that gamma interferon has activity, but it is not clear whether it is the same or slightly lower than that of alpha interferon.

Table II shows the summary of the results of these interferon trials. Overall, 56% of 126 patients responded to interferon, and 17% had a complete response. These results are similar to those achieved with combination chemotherapy. The overall response rate to alpha interferon (60%) was higher than gamma interferon (31%), although the prognostic characteristics of the single gamma interferon study were worse. Patients who were low stage and who had not previously received chemotherapy were more likely to respond to alpha interferon (69% versus 57%), especially with a complete response (41% versus 16%).

These trials establish the activity of recombinant alpha interferon in the cutaneous T-cell lymphomas. Nonetheless, a number of questions remain. Because a minority of patients achieve a complete response, should alpha interferon be combined with other therapies including chemotherapy, topical nitrogen mustard, psoralen and ultraviolet A light (PUVA), retinoids, or other experimental agents? In these combinations should the interferon be given concurrently with the other agents or after a response has been achieved? A number of studies have been designed to address these issues in cutaneous T-cell lymphomas as well as other related malignancies.

The groups from Northwestern University and the University of Colorado conducted a Phase I study of alpha interferon and PUVA. This study showed an extremely encouraging complete response rate (80%), with median response duration exceeding 18 months, and is reviewed by Roegnik elsewhere in this supplement [25]. Alpha interferon was evaluated in combination with 13-cis retinoic acid in a small series from Denmark and is under study [23] by the Southwest Oncology Group. The combination of alpha and gamma interferon is being evaluated in chronic myelogenous leukemia. If these trials yield encouraging results, the combination should be studied further in CTCL. Alpha interferon with chemotherapy and after chemotherapy-induced response is being evaluated in multiple myeloma and low-grade B-cell lymphomas. Alpha interferon is being combined with deoxycoformycin in hairy cell leukemia and in a CTCL trial at the National Cancer Institute. Subsequent combination studies in CTCL should be conducted based on combination results in these related low-grade lymphoproliferative malignancies.

Table II. Literature Review of Interferons in Cutaneous T-Cell Lymphomas

Reference	Author	Interferon[a]	No. of Patients	Prior Chemotherapy	Advanced Stage	Complete Response	Partial Response	% Response	Median Duration Response (range)
[16,17]	Bunn[b]	50MU TIW	20	16	15	3	9	45	6(3–36+)
[18]	Kohn[b]	10MU d1 50MU d2–5 q3w	24	19	17	1	6	29	8(4–19)
[19]	Olsen[b]	3MU qd or 3–36 MU qd	22	10	6	6	9	68	NR(4–28)
[21]	Tura[b]	3–18 MU/d	15	9	13	3	9	80	NR
[22]	Covelli[b]	3–18 Mu/d	20	0	5	8	9	85	12+
[20]	Vonderheid[c]	5 MU TIW ×4W	5	0	0	0	0	0	—
[23]	Thestrup-Pederson[b]	3–36 MU qd	4	0	1	0	3	75	4(3–12)
[24]	Kaplan[d]	0.25–0.5 mg/m² qd	16	11	11	0	5	31	10(3–24+)
	TOTAL		126	65	68	21	50	56%	
Summary									
Alpha interferon			110	54	57	21	45	60	
alpha low stage/no chemo[e]			29	0	6	8	12	69	
alpha high stage/chemo[f]			81	54	51	13	33	57	
Gamma			16	11	11	0	5	31	

[a] Dose/square meter body surface area.
[b] rIFNα2a.
[c] rIFNα2b.
[d] rIFNγ.
[e] Summary of studies with most patients having low stage and no prior chemotherapy.
[f] Summary of studies with most patients having advanced stage and prior chemotherapy.

Table III. Radiolabeled T101 Imaging in Cutaneous T-Cell Lymphomas

Antibody label	Route	Number of Patients	Nodes	Liver	Skin	Reference
111-In	IV[a]	11	11/11	11/11	5/6[b]	Carrasquillo [8]
131-I	IV[a]	4	2/4	4/4	0	Carrasquillo [10]
111-In	SQ[c]	11	44/44	8/11[a]		Keenan [9,11]
111-In	IL[d]	7	7/7	NR[e]		Mulshine [27]

[a] IV: intravenous.
[b] 5/6 in patients with cutaneous tumors or erythoderma; 0/5 in patients with plaque lesions.
[c] SQ: subcutaneous.
[d] IL: intralymphatic.
[e] NR: not reported.

MONOCLONAL ANTIBODIES

Royston and co-workers demonstrated that a 65-kd antigen (CD5) was present in normal T cells and nearly all malignant cells in patients with cutaneous T-cell lymphomas and chronic lymphocytic leukemias [26]. Commercial antigens reacting with this CD5 antigen were termed T101, Leu 1, and others. The first clinical studies of unlabeled antibodies were conducted at Stanford University by Miller and Levy [3,4]. They reported that small doses of Leu 1 could cause significant reductions in the number of circulating T cells in a patient with T-cell leukemia. Unfortunately, the reductions were transient in nature and the therapy did not lead to a sustained remission. The same authors reported that one patient with mycosis fungoides had a transient partial remission following Leu 1 therapy [4]. Larger series of patients were evaluated at the National Cancer Institute [5], the University of California–San Diego [6], and the University of South Carolina [7]. The results of these series are summarized in Table IV. Only five of 43 patients in these combined series had objective responses, and these were partial responses of brief duration. The lack of greater response was ascribed to several factors. i) The therapeutic dose required to achieve antibody binding to cells in tissue sites exceeded 1 mg. After lower doses most of the antibody was bound to antigen on circulating cells and circulating antigen. ii) There was rapid modulation (down regulation) of antigen. Complete antigen modulation occurred with 2 h of antibody administration and lasted up to 72 h. Antibody administration for more than 1 h was essentially useless because of antigen modulation. iii) Toxicity, perhaps due to T101 binding by normal T cells, prevented rapid antibody administration. iv) The ability to administer multiple antibody doses was limited by the development of human anti-mouse antibodies and allergic reactions. Although these trials did not lead to great therapeutic success, it was shown that T101 could be administered safely, could reach tumor cells in tissue sites, and was partially internalized as a consequence of antigen modulation.

Clinical trials with radiolabeled antibodies were a logical extension of these early trials, especially in light of the internalization (Table III). A DTPA chelate of T101 bound to 111-Indium was given to 11 CTCL patients in an NCI trial [8]. Successful imaging of nodal sites of disease was accomplished in 38 of 39 node sites in 11 of 11 CTCL patients. Additionally, 44 of 92 other node sites showed radiolabeled antibody uptake. Imaging of cutaneous disease was slightly less successful. Cutaneous tumors and erythroderma were successfully imaged in five of six patients [8]. However, cutaneous plaque lesions were not identified in any of five patients.

Considerable uptake was noted in the liver and spleen of all 11 patients evaluated in this study. Liver biopsies were negative for lymphatous involvement in some of these patients, suggesting the uptake was non-specific in nature. Control studies with a nonspecific 111 In-9.2.27 anti-melanoma antibody confirmed the nonspecific nature of the liver-spleen uptake. To avoid this non-specific uptake and to evaluate the utility of 111In-T101 immunolymphoscintigraphy for staging, we administered 111In-T101 to patients via the subcutaneous and intralymphatic routes [9–11,27]. For subcutaneous administration, 111In-T101 was injected between the webs of the toes in each foot [9,11]. Serial gamma camera images were then obtained. Excellent uptake was noted in the inguinal and femoral nodes of each patient. Uptake in more distant retroperitoneal and mediastinal lymph nodes was dose dependent. Up to 4.4% of the injected radioisotope per gram was found in the inguinal and femoral lymph nodes compared to about 0.02%/gm following intravenous administration. Far less radioisotope was observed in the liver and spleen following S.Q. administration, and this was also dose dependent.

The intralymphatic administration of T101 was accomplished at the same time that patients were given a standard lymphangiogram [27]. This route of administration also provided excellent imaging of femoral, inguinal, and retioperitoneal adenopathy with greater uptake/gm of tissue than following intravenous administration and with less hepatic uptake/gm of tissue than after intravenous administration. The ultimate clinical role of these techniques remains to be determined. Clinical evaluation of lymph nodes has provided useful information which has not been enhanced by standard lymphangiography. Lymph node biopsies from peripheral lymph nodes provides additional information, but retioperitoneal lymph nodes biopsies obtained at laparotomy have not yielded additional prognostic information. Thus, these radiolabeled antibody studies have provided useful biologic data for study but may not be clinically relevant in CTCL.

The success of 111In-T101 imaging studies suggested that higher doses of radioisotope might be employed with therapeutic intent. 111-Indium is an excellent isotope for imaging, but its photon emissions are not ideal for therapy. Thus, 131-Iodine and 125-Iodine labeled T101 were investigated. We showed that 125 I-T101 could specifically kill up to three logs of malignant human T-cell lines in in vitro soft agarose cloning experiments [28]. We next tested low-dose 131I-T101 for its utility in imaging tumor sites in CTCL patients [10]. Unfortunately, the imaging results from 131I-T101 were significantly inferior to those of 111In-T101. This was largely explained by the in vivo dehydrogenation of 131I from the T101.

Unaware of these results, Rosen and colleagues conducted a therapeutic trial employing 131I-T101 [29]. They found imaging results which were similar to the NCI experience with 131I-T101. They observed clinical antitumor effects in five of six patients, in-

Table IV. T101 Therapy in Cutaneous T-Cell Lymphomas

Unlabeled	Reference	Number of Patients	PR[a]	MR[b]
	Bunn [5]	12	0	3
	Miller [3]	9	4	0
	Miller [4]	14	0	6
	Dillman [4]	8	1	0
	Bertram [7]			
Total		43	5(12%)	9(21%)
131I Labeled	Rosen [29]	6	3(50%)	2(33%)

[a] PR: partial response.
[b] MR: minor response.

cluding partial responses in three patients and mixed or minor responses in two patients. Undoubtedly some of the anti-tumor effects were due to the specific localization of the 131I by the T101, but whole body irradiation from the dehalogenated 131I may also have contributed. None of the antitumor responses lasted more than 6 months. The main toxicity in this study was myelosuppression. This was undoubtedly due to the whole body irradiation of 131I, especially that which was dehalogenated. Better antitumor effects with less myelosuppression have been observed in B-cell lymphoma patients treated with 131I labeled anti-B-cell antibodies. In these instances there has been less dehalogenation of the radioiodine from the antibody. The majority of these patients achieved complete responses after a single dose of radiolabeled antibody. Currently, better antibody-isotope conjugates are being developed for further trials in T-cell lymphoma patients.

CONCLUSIONS

Recombinant alpha interferon is an active systemic therapy for the treatment of cutaneous T-cell lymphomas. Its activity as a single agent is similar to that of combination cytotoxic chemotherapy was less serious and more reversible toxicities. Recombinant alpha 2 interferons are more active in patients with low stages who are not heavily pretreated with other systemic therapies. It may also be less useful in patients who have converted to a high-grade malignancy. Despite the high response rates to recombinant alpha interferon, a minority of patients achieve a complete response and long-term, disease-free survival is unusual. Recombinant alpha interferon may be more useful when combined with other forms of therapy, including those directed at the skin, cytotoxic chemotherapy, and other biologic agents. Such combinations are under investigation, and preliminary results are presented elsewhere in this supplement.

Monoclonal antibodies have been evaluated for their role in the staging and treatment of cutaneous T-cell lymphomas. Unlabeled T101 and similar antibodies can be safely administered and may produce transient anti-tumor effects, especially of circulating cells. Their clinical utility is hampered by a number of factors, including the rapid internalization of the antigen it recognizes. Radiolabeled T101 is quite successful in imaging sites of lymphomatous involvement in CTCL patients when an optimal radioconjugate is employed. 131-T101 conjugates provide better anti-tumor responses than unlabeled antibody, although with far greater toxicity. Further advancement in this area awaits the development of better radioimmunoconjugates.

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